Enhancing response in the cardiac resynchronization therapy patient

Auricchio, Angelo ; Prinzen, Frits W

Abstract: Cardiac resynchronization therapy (CRT) is an established nonpharmacological treatment for patients with heart failure (HF), reduced left ventricular (LV) ejection fraction, and a wide QRS complex. Although the therapy was developed 30 years ago and approved by the Food and Drug Administration in 2001, attempts to improve it have never stopped. Such improvements have been facilitated by combining knowledge from bench (basic science), bits (computer modeling), and bedside (clinical studies); these issues are addressed in the present review. Improvements include better patient selection, positioning of the LV lead, pacing from multiple sites, and optimization of atrioventricular and ventriculo−ventricular intervals. Overall, patterns of electrocardiographic and echocardiographic (strain) signals appear to be more useful for patient selection than timing intervals (QRS duration, time-to-peak shortening). Quadripolar leads have significantly improved CRT outcome due to increased electrical and mechanical lead performance (avoiding phrenic nerve stimulation and improving lead stability), but also thanks to the flexibility offered by the novel leads to avoid in-scar pacing. The benefit of multiple site stimulation over optimal conventional biventricular pacing seems small and is awaiting evidence from large trials. There is rapidly growing interest in merging imaging information to guide positioning of the LV lead in late activated regions without scar and in LV lead positions other than the epicardial coronary veins (LV endocardium, His bundle, LV septum). All these developments look promising but await further clinical validation. Finally, computer modeling is rapidly becoming important in understanding the substrate for CRT, in improving and assisting patient selection, as well as in guiding therapy planning.

DOI: https://doi.org/10.1016/j.jacep.2017.08.005

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017

ISSN 2405-500X
http://dx.doi.org/10.1016/j.jacep.2017.08.005

STATE-OF-THE-ART REVIEW

Enhancing Response in the Cardiac Resynchronization Therapy Patient

The 3B Perspective—Bench, Bits, and Bedside

Angelo Auricchio, MD, PhD,[a] Frits W. Prinzen, PhD[b]

JACC: CLINICAL ELECTROPHYSIOLOGY CME/MOC

This article has been selected as the month's *JACC: Clinical Electrophysiology* CME/MOC activity, available online at www.jacc-electrophysiology.org by selecting the *JACC* Journals CME/MOC tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME/MOC activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME/MOC Certificate

To obtain credit for *JACC: Clinical Electrophysiology* CME/MOC, you must:

1. Be an ACC member or *JACC: Clinical Electrophysiology* subscriber.
2. Carefully read the CME/MOC-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME/MOC credit.
4. Complete a brief evaluation.
5. Claim your CME/MOC credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME/MOC Objective for This Article: Upon completion of this activity, the learner should be able to: 1) define the importance of pre-procedural cardiac imaging to evaluate scar location, and extension for targeting non-scarred areas for left ventricular pacing; 2) compare the impact of the use of left ventricular bipolar versus quadripolar lead, and explain the rationale for possibly using multisite pacing; and 3) explain the importance of adoption of automatic pacing chamber selection, atrioventricular-delay and ventriculo-ventricular-timing optimization algorithm.

CME/MOC Editor Disclosure: CME/MOC Editor Smit Vasaiwala, MD, has nothing to declare.

Author Disclosures: Dr. Auricchio has been a consultant to Medtronic, Boston Scientific, Biosense Webster, and LivaNova; and has received speaker fees from Medtronic, Boston Scientific, and LivaNova. Dr. Prinzen has received research grants from Medtronic, St. Jude Medical, LivaNova, Merck Sharpe & Dohme Corporation, Biotronik, and Biosense Webster.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC Term of Approval

Issue Date: November 2017
Expiration Date: October 31, 2018

From the [a]Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; and the [b]Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands. Dr. Auricchio has been a consultant to Medtronic, Boston Scientific, Biosense Webster, and LivaNova; and has received speakers' fees from Medtronic, Boston Scientific, and LivaNova. Dr. Prinzen has received research grants from Medtronic, St. Jude Medical, LivaNova, Merck Sharpe & Dohme Corporation, Biotronik, and Biosense Webster.
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received June 6, 2017; revised manuscript received August 2, 2017, accepted August 10, 2017.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1203–19

Enhancing Response in the Cardiac Resynchronization Therapy Patient

The 3B Perspective—Bench, Bits, and Bedside

Angelo Auricchio, MD, PhD,[a] Frits W. Prinzen, PhD[b]

ABSTRACT

Cardiac resynchronization therapy (CRT) is an established nonpharmacological treatment for patients with heart failure (HF), reduced left ventricular (LV) ejection fraction, and a wide QRS complex. Although the therapy was developed 30 years ago and approved by the Food and Drug Administration in 2001, attempts to improve it have never stopped. Such improvements have been facilitated by combining knowledge from bench (basic science), bits (computer modeling), and bedside (clinical studies); these issues are addressed in the present review. Improvements include better patient selection, positioning of the LV lead, pacing from multiple sites, and optimization of atrioventricular and ventriculo–ventricular intervals. Overall, patterns of electrocardiographic and echocardiographic (strain) signals appear to be more useful for patient selection than timing intervals (QRS duration, time-to-peak shortening). Quadripolar leads have significantly improved CRT outcome due to increased electrical and mechanical lead performance (avoiding phrenic nerve stimulation and improving lead stability), but also thanks to the flexibility offered by the novel leads to avoid in-scar pacing. The benefit of multiple site stimulation over optimal conventional biventricular pacing seems small and is awaiting evidence from large trials. There is rapidly growing interest in merging imaging information to guide positioning of the LV lead in late activated regions without scar and in LV lead positions other than the epicardial coronary veins (LV endocardium, His bundle, LV septum). All these developments look promising but await further clinical validation. Finally, computer modeling is rapidly becoming important in understanding the substrate for CRT, in improving and assisting patient selection, as well as in guiding therapy planning. (J Am Coll Cardiol EP 2017;3:1203–19)

Heart failure (HF) is a significant health problem that affects nearly 20 million people worldwide, with a projected 25% increase in prevalence by 2030. Related expenditures are expected to more than double by the same period (1). Despite significant advances in pharmacological therapy, morbidity and mortality remain high (2). Ventricular conduction disturbance, most commonly left bundle branch block (LBBB), is present in approximately one-third of HF patients, and leads to loss of synchrony of contraction of the ventricles. Consequently, these patients are at higher risk of HF hospitalization and death.

In 1987, Dr. Morton Mower filed a patent application for the concept of "biventricular pacing" after a pre-determined atrioventricular (AV) interval explicitly aimed at HF failure treatment. This concept, later termed cardiac resynchronization therapy (CRT), is currently an established nonpharmacological treatment for patients with HF, reduced left ventricular (LV) ejection fraction, and a wide QRS complex (3,4). It has been revolutionary for patients with advanced HF whose only previous option was cardiac transplantation, and it is now a realistic option for patients with mild HF (3,4). CRT remains the only therapy for HF that simultaneously improves cardiac function and functional capacity, reduces hospitalization, and prolongs survival (**Figure 1**). The large range of benefits among patients, spanning from complete normalization of ventricular volume and ejection fraction to a complete lack of benefit, has triggered significant research activities to de-convolute the biological and mechanistic aspects for CRT inefficacy, some of which are discussed in the present review and are illustrated in **Figure 2**. From the beginning, research in the field of CRT has been characterized by a bedside-to-bench and back again approach, whereas during the last decade, computer models have provided rapidly increasing additional insights. Therefore, this review discusses the combination of "bench, bits, and bedside" (which we named "the 3B perspective") by considering that the combination of these 3 factors may bring the field forward.

PATHOBIOLOGY OF CRT

Dyssynchrony and its correction by CRT induces a wide range of changes beyond the direct electrical and mechanical effects, many of which are unique to the disease. The seminal work by the Baltimore group showed that dyssynchronous HF is characterized by maladaptive remodeling processes at all levels, ranging from the genome to the proteome, transcriptome, metabolome, and is visible at the cellular level, translating to the phenotype (9). Altogether, these abnormalities have been referred as dyssynchronopathy (9). In dyssynchronous HF, most of the defects are specific to early- or late-activated myocardial territories, including processes like hypertrophy and related expression of microRNAs (10). CRT can correct most of these defects by mechanisms that are still not completely elucidated.

Although little information is available on the tissue changes in human dyssynchronous hearts, several clinical trials showed that patients with LBBB in the control arms had a worse prognosis than patients with otherwise similar degrees of HF but no LBBB (11). In contrast, once treated by CRT, the LBBB patients had an improved outcome beyond that of other patients, supporting an idea that originated from animal experiments on extensive cellular and molecular recovery. Clinical data were limited to reductions in cavity dimensions and levels of circulating plasma markers of inflammation, such as apoptotic signaling of fibrosis. Some studies indicated that, upon turning CRT off after several months, intrinsic QRS duration was reduced (12), which might be explained by the reduction in fibrosis or modification in myocardial tissue architecture, gap junction expression, myocardial hypertrophy and/or smaller ventricular chambers. Clearly, more information on myocardial changes during clinical application of CRT would be welcome, if only because understanding these changes could also be beneficial to the treatment of other pathologies.

PATIENT SELECTION: DEVELOPING VIEWS ON USE OF ELECTROCARDIOGRAPHIC CRITERIA

QRS duration and a LBBB morphology of the QRS complex are currently considered the most reliable biomarkers for selecting candidates for CRT. According to clinical practice guidelines by all scientific societies in cardiology, CRT eligibility includes a QRS duration of >120 ms and LBBB morphology (3,4). Clinical practice guidelines may recommend CRT in patients with a QRS duration of <150 ms only when a clear LBBB morphology of the QRS complex is diagnosed (3,4). However, electrocardiography (ECG) criteria to classify LBBB significantly differ among scientific organizations, investigators, trials, and guidelines, which may pose uncertainty in meta-analytical analysis and comparison of outcomes. Notably, ECG definitions for LBBB have never been designed to predict response to CRT.

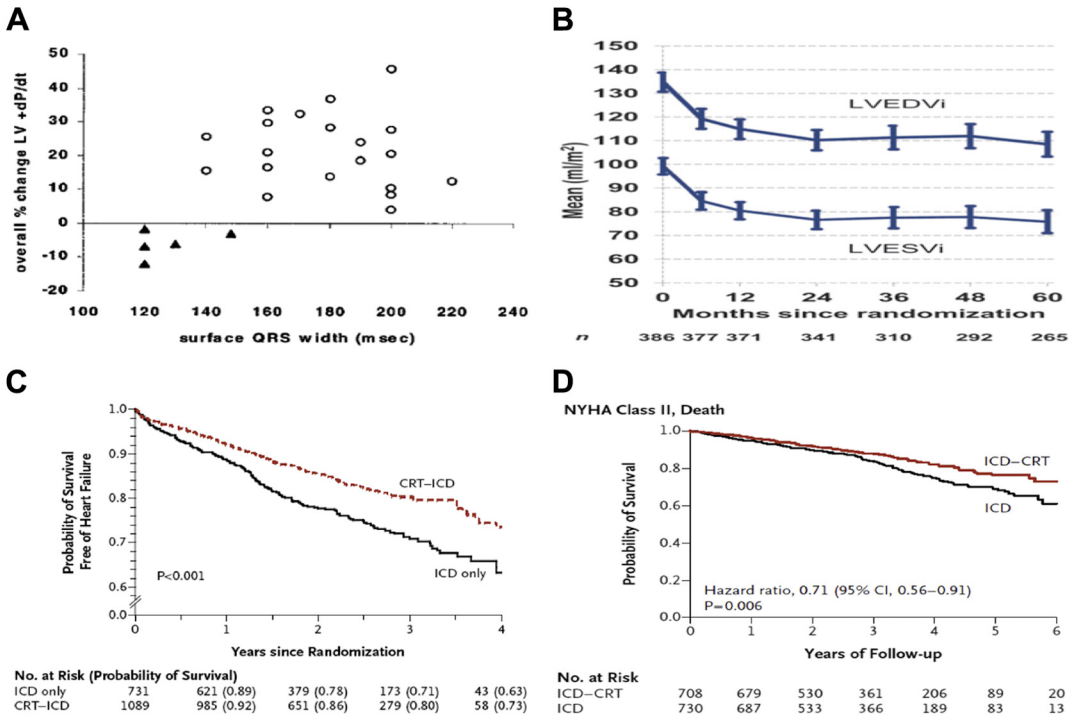
The challenge usually pertains to the detection of QRS slurring and notching to identify LBBB. There is no standard definition of QRS notch and slur patterns in modern quantitative ECG; this is likely because definitions are difficult to apply manually by clinicians because physicians rely on small amplitude and duration measurements. Measuring and interpreting the QRS complex from a standard 12-lead ECG is a lengthy and tedious process, especially if the patient has an underlying disease (e.g., previous myocardial infarction or myocardial hypertrophy), which may further alter the morphology and duration of QRS. Although the QRS delineation and duration are believed to be usually easier to be determined than notching and slurring, recent reports have indicated large interobserver and intraobserver variability in manual reading (13), as well as limited accuracy and precision of automated measurements of QRS duration among ECGs (14). The difference could exceed the level of 10 to 15 ms, which might be considered clinically significant for qualifying a patient for CRT or for providing a class of recommendation for CRT (14). Interestingly, there is limited literature on the correlation of a specific morphological marker associated with intraventricular conduction disturbance, LBBB, or right bundle branch block (RBBB) with clinical in vivo measurements of intracardiac activation times. Also, the threshold of 120 ms that indicates an abnormal QRS duration was established based on a pattern recognition that compared dogs with humans, not on objective measurements in humans (15).

Although most patients treated with CRT have a LBBB QRS morphology, since the introduction of CRT into clinical practice, a growing number of patients with RBBB QRS morphology or intraventricular conduction abnormalities have also been treated. A recent review reported that an average of 18% of all treated CRT patients had RBBB, with a variable proportion ranging from 5% to 26% (16). Thus, these patients represent a sizeable subgroup in need of adjunct therapies on top of the best pharmacological therapy. The available evidence indicates that straightforward

ABBREVIATIONS AND ACRONYMS

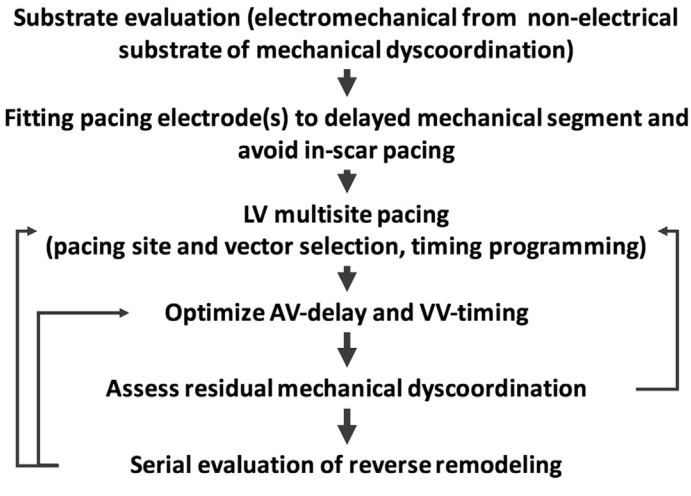
AV = atrioventricular
BiV = biventricular
CI = confidence interval
CMR = cardiac magnetic resonance
CRT = cardiac resynchronization therapy
ECG = electrocardiography
ECGi = electrocardiographic imaging
HF = heart failure
HR = hazard ratio
LBBB = left bundle branch block
LV = left ventricle
LV dP/dtmax = first derivative of left ventricular pressure
RBBB = right bundle branch block
RV = right ventricle
VCG = vectorcardiography
VV = ventriculo-ventricular

FIGURE 1 Compilation of the Various Effects of CRT



(A) Acute hemodynamic effect as reported by the PATH-CHF study (adapted from Auricchio A, et al. [5]). **(B)** Reverse remodeling as described in REVERSE study (adapted from Linde C, et al. [6]). **(C)** Reduction in hospitalization for heart failure as shown by MADIT-CRT (adapted from Moss A, et al. [7]). **(D)** Reduction in mortality as reported by the RAFT trial (adapted from Tang et al., [8]). CRT = cardiac resynchronization therapy; CI = confidence interval; ICD = implantable cardioverter-defibrillator; LV dP/dtmax = first derivative of left ventricular pressure; LVESVi = left ventricular end-systolic volume index.

FIGURE 2 Key Elements of Modern Use of CRT in Heart Failure Patients



AV = atrioventricular; VV = ventriculo-ventricular; other abbreviations as in Figure 1.

application of CRT in patients with RBBB should be discouraged (16). However, in vivo mapping data and in silico simulation indicates that there is a subset of patients with RBBB who may benefit from CRT; these patients are characterized by a QRS morphology on limb leads that resemble a LBBB and show delayed LV activation, particularly of the LV free wall (17). Thus, an individualized treatment strategy in RBBB is of utmost importance and should be used based on the presence of LV and right ventricular (RV) dyssynchrony demonstrated either by advanced echocardiographic techniques (18) or by the surface ECG (17). Admittedly, the treatment options for these patients with RBBB, previously proposed by us, have been mechanistically developed (12), and may require confirmation in larger prospective studies.

Therefore, due to all of the previously indicated limitations of surface ECG in precisely defining bundle branch block and reliable prediction of CRT response, other ECG-derived indexes may be worth considering.

TABLE 1 Commercially Available Pacing Algorithms for Single-Lead Left Ventricular Multipoint Pacing and Possible Pacing Configurations

Feature Name	Boston Scientific MultiSite Pacing	St. Jude Multipoint Pacing	Medtronic Multiple Point Pacing	Biotronik MultiPole Pacing
CE Mark Status	Established 1Q 2017	Approved	Approved	Approved
Pacing Vectors Available	17	10	5	12
LVa - LVb Timing Offset	Independent cathodes 0–100 ms	Independent cathodes 5–80 ms offsets	Tied cathodes, no offsets	Independent cathodes 0–50 ms
Automatic Programming Recommendation	Yes SmartVector algorithm automatically recommends settings	Yes Options for choosing based on RV-LV or widest spacing	None for MPP	Unknown
Pacing Configurations	Bi-V LV only	Bi-V	Bi-V LV only	Bi-V

CE = European Commission; Bi-V = biventricular; LV = left ventricular; MPP = MultiPoint Pacing; RV = right ventricular.

BEYOND CONVENTIONAL 12-LEAD ECG. Of all the characteristics of a LBBB-like conduction abnormality, delayed activation of the LV is likely crucial for a heart to be amenable to CRT (19). This inferred abnormality is supported by studies that showed that a greater delay in time from onset of the QRS complex to local LV activation at the LV stimulation site (Q-LV) was associated with a greater likelihood of benefit from CRT (20). The most accurate way to determine late LV activation is to directly measure it (21), which requires an invasive procedure. Although it can be performed during a CRT implantation procedure (20), the decision whether to implant a device should be made in advance. ECG imaging (ECGi) provides a valuable noninvasive alternative to direct measurement (22). ECGi provides high-resolution noninvasive electrical mapping of the epicardial electrical activation, and requires a computed tomographic scan and positioning of a few hundred electrodes on the body surface. A recent study provided extensive validation of this technique in animal hearts with pacing-induced dyssynchrony. This study pointed to the important role of a proper spatio-temporal approach that considers characteristics of neighboring electrograms (23). Ploux et al. (22) showed that the mean electrical delay between the RV and LV provides good prediction of CRT response. A recent, simpler alternative was presented, in which an ECG belt with 53 electrodes was used to characterize the electrical heterogeneity of the ventricles (24).

A different approach may be the use of vectorcardiography (VCG), synthesized from the regular 12-lead ECG (25). A VCG-derived area of the QRS complex (QRS area) strongly predicted late activation of the LV, even in RBBB (26). QRS area was shown to be a good predictor of echocardiographic CRT response, performing at least as well as LBBB and outperforming both QRS duration >150 ms and LBBB (27). Other studies also showed that T-wave area and the sum of QRS and T-wave area provided good prediction of CRT response (28). The fact that these measures can be obtained using routine ECG measurements makes them good candidates for widespread use soon.

MECHANICAL MARKERS OF DYSSYNCHRONY

The working mechanism of CRT is complex and still not completely understood. Part of this complexity comes from the fact that CRT is primarily designed for correction of an electric substrate (originating from conduction disorders), but it exerts its effects mainly through correction of mechanical inefficiency. Because of the heterogeneous overall response in accordingly selected patients, mechanical dyssynchrony has been proposed as an additive selection criterion.

Although simple echocardiographic markers like apical rocking, septal flash, and interventricular mechanical dyssynchrony appear valuable in identifying patients who would most likely benefit from CRT (29), more sophisticated echocardiographic indexes of mechanical dyssynchrony were tested in the early 2000s. Large randomized trials that used different echocardiographic indexes consistently reported disappointing results. A good example of a negative study in the field is the EchoCRT study. This study selected patients with narrow (<130 ms) QRS complexes and mechanical dyssynchrony that were identified by interventricular mechanical delay and/or longitudinal strain. Patients who received biventricular (BiV) pacing actually showed a worse outcome, including significantly higher mortality compared with patients in the control group (30). The subgroup of patients with low global longitudinal strain showed a particularly poor clinical outcome, which indicated the harmful effect of improperly

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1203–19

applied CRT in combination with poor myocardial contractile function (31).

A more promising picture appeared for strain-based parameters of mechanical dyssynchrony applied in patients with a wider (>130 ms) QRS complex. Several large, recent observational studies that used advanced echocardiographic measurements, including speckle tracking–derived indexes, showed an improvement in the prediction of echocardiographic CRT response on top of QRS duration and QRS morphology when they analyzed time-to-peak values (18,32,33). Even better predictions were achieved when considering the regional differences in morphology of strain curves (34,35) (see the following on Computer Modeling). Such regional differences in morphology of strain curves are helpful to distinguish LBBB-like conduction abnormalities that are amenable to correction by CRT from ventricular conduction disturbance-like ones, which, in contrast, are unlikely to respond to CRT. The same concept applies to patients with RBBB, in whom the presence of regional differences of strain curves resembling a LBBB-like pattern most likely point to a positive response to CRT (18).

DEVELOPMENTS IN DELIVERY OF CRT: TARGETED LEAD PLACEMENT, MULTISITE PACING, AND MULTIPOINT PACING. During the last decade, improved physiopathological knowledge and significant technological advancement have resulted in LV placement guided by multimodality imaging, more appropriate selection of LV epicardial pacing sites via the coronary sinus, possible multiple site pacing, and multipoint LV pacing. According to common terminology, multisite pacing is obtained by using 2 leads in 2 different coronary veins or 2 separate RV sites, whereas multipoint pacing is delivered using multiple electrodes on a single LV lead (**Table 1**). The concept of multisite–multipoint pacing is based on the hypothesis that pacing at multiple locations within the ventricles electrically engages a larger ventricular mass and will therefore improve cardiac resynchronization.

TARGETED LEAD PLACEMENT. Beside the substrate for resynchronization, a primary point of interest is the site of LV pacing, because this is likely to determine the degree of resynchronization. The presence, location, and burden of myocardial scar and the position of the LV lead with respect to these regions are key determinants in CRT response. Implantation of a LV lead in an area of myocardial scar may be associated with slow conduction and block, resulting in less hemodynamic improvement and poor clinical outcome.

A few published studies investigated whether a greater response to CRT could be achieved through targeted delivery of LV leads to late-activated segments free of scar. The STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) study, performed with the 17-segment echocardiographic model, indicated good CRT response when the LV lead was truly concordant with or in any of the 8 LV segments adjacent to the last-activated segment (36). In this study, segments with echocardiographic evidence of scarring were excluded from analysis. Similarly, in the TARGET (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy) study, considerable benefit from CRT was derived from positioning the LV lead away from regions with low strain, which suggested scarring (37). Pacing in a scarred region was associated with a 6-fold increased risk of cardiovascular death or combined cardiovascular death and hospitalization for HF compared with pacing in regions with no scarring (38). Therefore, current evidence points more to the importance of avoiding LV lead positioning in a scarred region than positioning it in the latest activated region, and eventually to a more systematic assessment of the presence, location, and extension of myocardial scar by different cardiac imaging techniques.

Further studies investigated a more advanced use of imaging for road mapping of LV lead placement. Bakos et al. (39) showed the feasibility of using a combination of echocardiographic speckle tracking and cardiac magnetic resonance (CMR) to guide placement of the LV lead to prescribed targets. Procedural success, defined as lead delivery to the prescribed or immediately adjacent segment, was 95%. More recently, Behar et al. (40) tested the feasibility of a purpose-built integrated software platform to process, analyze, and overlay CMR data in real-time within a hybrid X-CMR environment to guide LV lead implantation. These authors contemporaneously used gold standard myocardial imaging to avoid scar regions while targeting late activating segments, thereby permitting imaging-guided LV lead implantation in a single procedure. Despite the best-in-class imaging and lead technology for guiding quadripolar LV lead implantation, in 4 patients (28%), a CMR-defined target segment (based upon avoiding scar and targeting a late mechanical activated segment) could not be reached due to lack of an appropriate coronary vein. This resulted in the placement of a quadripolar LV lead adjacent to or in the scar. This observation strongly suggests that further improvement in alternative lead positioning is needed

(see Emerging Technologies for Resynchronizing the Heart).

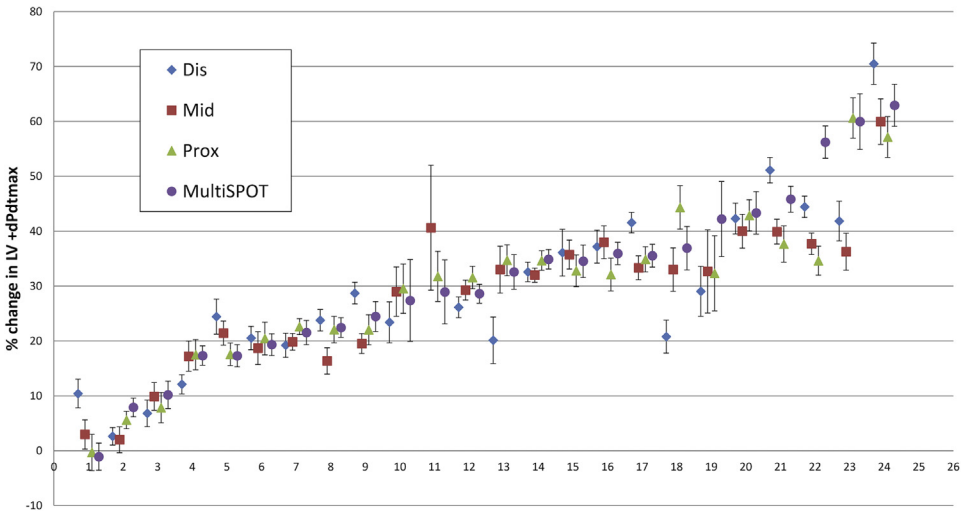
MULTISITE CRT. The concept of triple-site pacing is interesting, but one of the limitations is that this pacing modality has been evaluated only in small studies with soft endpoints, with the exception of the recent study by Providencia et al. which reported all-cause mortality and frequency of ventricular arrhythmias (41). Moreover, these studies are heterogeneous as far as patient selection (nonresponder to CRT vs. de novo patients), intrinsic rhythm (sinus rhythm vs. atrial fibrillation), and strategy for placing double LV leads is concerned; thus, comparing their results is somewhat challenging.

The TRIP-HF (Triple Resynchronization in Paced Heart Failure Patients) trial compared conventional CRT to BiV stimulation with 1 RV and 2 LV leads in 42 patients (42). This study showed a modest but significant improvement in LV ejection fraction and LV end-systolic volume, whereas there was no clinical benefit of triple-site pacing over BiV pacing. Lenarczyk et al. (43) performed a randomized trial in 44 patients and showed that after 3 months of CRT, triple-site pacing (double left-single right pacing site) was associated with a larger improvement in New York Heart Association functional class, an increase in oxygen consumption, and an increase in the 6-min walking distance than conventional CRT. The ejection fraction was also higher, and intraventricular synchrony was smaller in the triple-site pacing group than in the conventional CRT group. Rogers et al. (44) investigated 43 CRT patients in a double-blind crossover trial. Pacing leads were positioned in the RV apex and a lateral coronary sinus branch, with a third ventricular lead implanted in a further lateral coronary sinus branch in 23 patients and in the high RV septum in 20 patients. Devices were programmed in a randomized order to 4 pre-determined pacing configurations: conventional BiV, triventricular, dual-site and single-site left BiV, or RV pacing for a 3-month period with clinical and echo assessment at the end of each period. Compared with BiV pacing, triventricular pacing resulted in significant improvements in the 6-min walking distance (451 ± 112 m vs. 425 ± 119 m; $p < 0.008$), quality of life (32 ± 19 vs. 38 ± 24; $p < 0.036$), LV end-systolic volume (158 ± 79 ml vs. 168 ± 76 ml; $p < 0.05$), and ejection fraction (30 ± 8% vs. 27 ± 8%; $p < 0.05$). The most recent study by Providencia et al. (41) is a single-center, propensity score-matched study that compared the long-term clinical outcomes of 34 patients implanted with triventricular devices and BiV devices. Triventricular-treated patients, compared with BiV-treated patients, presented with a trend for shorter battery longevity. Incidence of lead dislodgment, device-related infection, and refractory phrenic nerve capture was comparable in the 2 groups. All-cause mortality and need for heart transplantation was lower in the triventricular-treated group compared with conventional CRT. In contrast, episodes of ventricular arrhythmia that required implantable cardioverter-defibrillator intervention occurred more frequently in the BiV group versus the triventricular group. This latter observation was in line with the findings reported by Ogano et al. (45), who showed a reduction of ventricular arrhythmias that required appropriate therapies in triple-site pacing compared with conventional CRT.

In summary, studies on pacing using multiple leads on the RV or LV showed that it is feasible, with an implantation success rate of approximately 85% to 95%. However, the overall implantation duration and fluoroscopic exposure might be longer than for conventional CRT (43,44). Furthermore, the statistical power of these studies is limited, and there is currently not enough evidence to consider this pacing modality as a first-line therapy. Further prospective clinical investigations are needed, with a clear evaluation of the clinical benefit and adverse events. The rate of complications of 2 LV or RV pacing deliveries have to be addressed in large trials that include lead extraction-related issues, as does the impact of decreased battery longevity. The currently available complication rate with dual-vein LV pacing cannot be generalized to other centers because centers undertaking multisite pacing are usually high-volume centers that report high success rates. There are 3 currently ongoing randomized, prospectively designed, controlled trials (TRIUMPH CRT [Triple-site Bi-Ventricular Stimulation in the Optimization of CRT; NCT02350842], STRIVE HF [Standard Care Versus Tri-Ventricular Pacing in Heart Failure; NCT02529410], and Efficacy and Safety of Multisite Cardiac Resynchronization Therapy; NCT01966016). These are feasibility studies that are assessing the improvement in echocardiography parameters with triventricular devices. Finally, although preliminary small studies have shown interesting results with triple-site pacing, clinicians should consider that the present clinical comparator is no longer represented by conventional CRT with a bipolar LV lead. In contrast, delivery of modern CRT is based on multipolar leads connected to a device capable of multipoint LV pacing using sophisticated AV and ventriculo-ventricular (VV) automatic programming algorithms (see section on Multipoint CRT).

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1203–19

FIGURE 3 Effect of Patient and Pacing Site Selection on Effect Size of CRT



Data from the iSPOT study: the acute change in LV dP/dtmax between patients ranged between approximately 0% and approximately 60%, whereas differences in change of LV dP/dtmax within a patient varied only by approximately 10%. Dis, Mid and Prox indicate biventricular pacing using the distal, mid, or proximal sites on the quadripolar LV lead, whereas Multispot indicates pacing from all sites together. Abbreviations as in Figure 1. Adapted from iSPOT (Left Ventricular Multispot Pacing for CRT) study (53), courtesy of Richard Cornelussen, Medtronic.

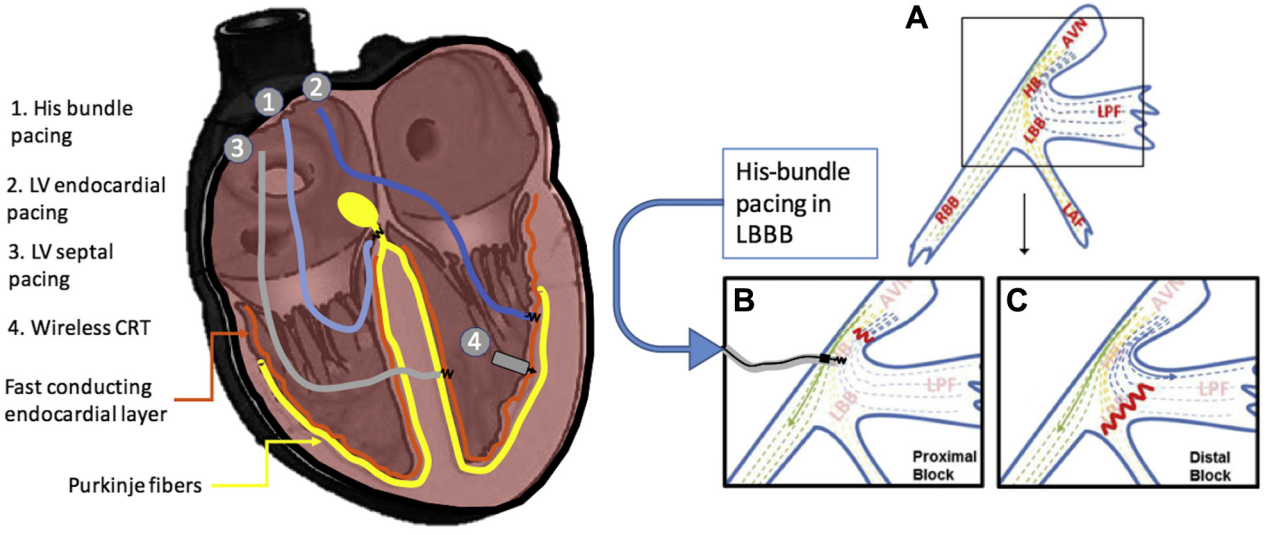
MULTIPOINT CRT. In contrast to multisite pacing, multipoint pacing has been made easily achievable by development of a LV quadripolar lead and by the concurrent development of CRT devices that are capable of multiple electrical outputs that allow different pacing vectors and timing delays between LV pacing sites (Table 1). The use of a quadripolar lead has already improved patient outcome and even survival compared with a conventional bipolar LV pacing lead due to fewer requirements for lead replacement and elimination of phrenic nerve stimulation (46,47). Transvenous procedural success with novel quadripolar lead design is currently achieved in up to 98% of cases. The use of a quadripolar lead that enables dual LV site pacing (multivector pacing configuration) is associated with a lower risk of deactivation (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.46 to 0.84; $p < 0.002$), replacement (HR: 0.67; 95% CI: 0.55 to 0.83; $p < 0.001$), and death (HR: 0.77; 95% CI: 0.69 to 0.86; $p < 0.001$).

Several studies suggested that multipoint pacing (i.e., multivector pacing), all or not combined with additional timing delays among different LV pacing sites, might create additional benefits compared with traditional dual-site LV pacing. Acute hemodynamic studies showed a significant but small increment of first derivative of LV pressure (LV dP/dtmax) (by 2% to 5% points) and stroke volume (by ~5%) (48,49). Small studies also showed a moderately better echocardiographic and clinical response (50,51). Further support for the benefit is being investigated in larger multicenter trials.

The MPP (MultiPoint Pacing) trial was a prospective, randomized, double-blind, controlled study to evaluate the safety and efficacy of CRT using a quadripolar lead for multipoint pacing compared with standard Bi-V pacing. Standard Bi-V pacing was activated at implantation. Then, at 3 months post-implantation, patients in whom the echocardiographic parameters during MPP were equal or better than during BiV pacing were randomized (1:1) to either an MPP or BiV arm. Preliminary results indicated that the primary safety endpoint was met with a 93.2% freedom from system-related complications. The primary efficacy endpoint was met by demonstrating noninferiority of the response rate in the MPP technology group compared with the BiV pacing group at 9 months compared with 3 months. Additional analyses demonstrated the ability of multipoint technology to achieve an 87% response rate in patients with optimal program settings (52).

Data that somewhat contradict those of the aforementioned studies came from the iSPOT (Left Ventricular Multispot Pacing for CRT) study. This study compared the acute hemodynamic response of the MPP study by using 3 electrodes on a quadripolar lead compared with conventional BiV pacing (53). Patients with LBBB underwent an acute hemodynamic

FIGURE 4 Illustration of the Novel Pacing Approaches in CRT



(Left) Illustration of the 4 novel pacing approaches in CRT: 1. His bundle pacing, 2. LV endocardial pacing, 3. LV septal pacing, 4. Wireless pacing in the LV endocardium. The fast conduction layer along the right ventricular and LV endocardium is depicted in **orange** and the Purkinje system is depicted in **yellow**. **(Right) (A)** Proposed mechanism of the benefit of His bundle pacing in the left bundle branch block (LBBB). The His bundle the fibers for the right bundle branch(RBB) and LBB are longitudinally dissociated so that in case of **(B)** proximal block, pacing in the His bundle can capture fibers in the LBB. **(C)** This option is likely not beneficial in case of distal block. AVN = atrioventricular node; HB = His bundle; LAF = left anterior fascicle; LPF = left posterior fascicle; other abbreviation as in Figure 1. Adapted from Teng et al. (65).

study to determine the percentage change in LV +dP/dtmax using a solid experimental design with repeated (4 times) measurements at 5 different AV delays. The percentage change in LV +dP/dtmax for pacing of all of the 3 electrodes together was not significantly superior to any conventional BiV pacing configuration (Figure 3). Notably, there was a large interpatient variability, with acute hemodynamic responses ranging from approximately zero to +60% (patients 11 and 17, respectively) (Figure 3). However, the difference in response among different pacing sites was usually approximately 10%. This indicated that patient selection was a more important determinant of CRT response than (epicardial) LV lead positioning and number of pacing sites. The authors concluded that, in patients with LBBB, MultiSPOT LV pacing demonstrated comparable improvement in contractility to the best conventional BiV pacing. The reasons for the conflicting outcomes between the iSPOT and other observational MPP studies, as well as the MPP randomized study, might be found in the use of different pacing vectors, the use of delays between stimulation of different leads, and inclusion of AV optimization in the iSPOT study. Additional statistical bias in favor of multipoint pacing might be created by the comparison of the best of several multipoint pacing options versus a single conventional BiV pacing setting. Thus, at present, the clinical value of any multiple site pacing mode is still not entirely clear. Finally, the fact that stimulating additional pacing electrodes reduces device battery longevity should be taken into consideration.

EMERGING TECHNOLOGIES FOR RESYNCHRONIZING THE HEART: ENDOCARDIAL PACING, TRANSSEPTAL PACING, AND HIS BUNDLE PACING

The common denominators for emerging technologies for resynchronizing the heart aim at creating activation patterns that are more physiological than transvenous CRT; they do not aim at positioning the lead in the latest activated region (Figure 4).

LV endocardial pacing has been proposed and has been shown to be superior to conventional LV epicardial pacing in the CRT setting in computer simulations (54) and preclinical experiments (55,56). In various canine LBBB models, superiority has been shown in electrical resynchronization and acute hemodynamic response (55,56). However, clinical studies showed less reproducible differences. Derval et al. (57) was not able to show significantly better hemodynamic

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1203–19

response between pacing in the endocardial position and immediately below the position of the coronary sinus lead, although in each patient there was an endocardial position that resulted in superior improvement in pump function. Similarly, Spragg et al. (58) found that endocardial pacing tended to be superior to epicardial pacing in patients with ischemic cardiomyopathy, but that the location of optimal LV endocardial pacing varied among patients. Shetty et al. (59) showed that LV endocardial pacing was superior to epicardial pacing and that it performed at least as well as CRT using multiple- or single-quadripolar epicardial leads. Although conceptually promising, practical implementation of long-term endocardial CRT using conventional pacing leads is still problematic, because currently leads placed in the LV cavity require anticoagulation and show significant dislodgement. Despite long-term anticoagulation therapy, the risk of stroke was substantial in the ALSYNC (Alternate Site Cardiac Resynchronization) study (60). ALSYNC evaluated the feasibility and safety of LV endocardial pacing using a market-released pacing lead implanted via a single pectoral access by a novel atrial transseptal lead delivery system. This study observed 14 transient ischemic attacks (n = 9, 6.8%), 5 nondisabling strokes (n = 5, 3.8%), and 23 deaths (17.4%).

A promising novel approach may be wireless pacing. Auricchio et al. (61), in a cohort of 17 patients, showed the feasibility of providing endocardial stimulation for CRT with a leadless, wireless technology. The more recent SELECT-LV (Safety and Performance of Electrodes Implanted in the Left Ventricle) study extended the data of this wireless CRT approach, which resulted in a population of patients in whom conventional CRT failed. This study showed an improvement in the clinical composite score in 85% of patients, and a positive echocardiographic response (reduction in left ventricular end-systolic volume >15%) in 52% of patients at 6 months (12). These clinical outcomes compared quite favorably with the clinical and structural improvements observed in conventional CRT trials.

His bundle pacing is a somewhat surprising option to create resynchronization. The option can only be effective if the bundle branch block is proximal, which fits with older studies that suggested that fibers of the right and left bundle branch might already be divided inside the AV node (62) (**Figure 4**, right panel). Depending on the nature of the LBBB, a completely narrow QRS may be achieved by direct His pacing. In the best option, direct His pacing is achieved with low stimulation strengths, but if the lead is not positioned inside the His bundle, the virtual pacing electrode may capture the conduction distally when the pacing output is high. Direct His bundle pacing in CRT candidates has been recently proposed and clinically tested in small patient cohort studies as summarized by Upadhyay and Tung (63) and Sharma et al. (64). Overall, there is a relatively consistent benefit with His-paced therapy. The 2 largest single-center case series of His bundle pacing for CRT-eligible patients have been published by Teng et al. (65) and by Ajijola et al. (66). Electrical resynchronization via His bundle pacing was consistently achieved in approximately 70% of patients who presented with bundle branch block with CRT indication. Interestingly, in nearly all patients, QRS narrowing was demonstrated by nonselective His capture, which resulted in an improvement in LV ejection fraction, reduction in size of the LV, and improvement in New York Heart Association functional class at least as much as during BiV pacing.

Transseptal LV endocardial pacing is the most recent development to pace LV. In this approach, the LV lead is introduced into the RV and subsequently advanced through the interventricular septum to reach the LV side of the septum (**Figure 4**). This approach likely avoids any coagulation problems, because there is no contact between the electrode and blood in the LV cavity. Studies in animals have shown that LV septum pacing yields LV pump function and contractile coordination that closely approximates that during normal ventricular conduction and is significantly better than that during RV septal pacing, even in the chronic setting (67). Recently, Mafi-Rad et al. (68) demonstrated that permanent implantation of a pacing lead with an extended helix in the LV septum using a transvenous approach through the interventricular septum is feasible and safe, at least in a small group of patients. In these patients with sick sinus disease, LV septal pacing reduced electric dyssynchrony and preserved LV pump function compared with RV septal and RV apex pacing. Electric and mechanical lead properties of this prototype lead remained stable during 6-month follow-up. Notably, LV septal pacing may avoid deterioration of LV function due to long-term RV pacing in patients with bradycardia, but data from animal studies suggest that it might also be an alternative to BiV pacing (69).

NOVEL PACING ALGORITHMS FOR AUTOMATIC SELECTION OF ATRIOVENTRICULAR AND VV DELAY

Since the early days of CRT, appropriate selection of AV delay and VV timing has been considered an

important factor to improve stroke volume. Several studies assessed the efficacy of ECG algorithms, echocardiography, or invasive assessments to determine ideal settings of AV delay and VV timing. Past clinical trials most commonly used a so-called "static programming approach" for AV delay and VV timing optimization (i.e., early assessment of each timing followed by infrequent adjustments over follow-up). This programming strategy was the result of the technological limitation in repeatedly evaluating AV delay and VV timing. As result, an electrogram-based algorithm and echocardiography to determine optimal AV activation did not demonstrate clinical superiority for the endpoint of LV end-systolic volume (70,71). In contrast, recent controlled randomized studies, the RESPOND-CRT (Clinical Trial of the Sonrtip Lead and Automatic AV-VV Optimization) and the AdaptivCRT (aCRT) algorithm (Medtronic, Inc., Mounds View, Minnesota), using a so-called "dynamic programming approach," suggested significant benefit of patient-specific continuous optimization of AV delay and VV timing, and a paced chamber (72,73).

The RESPOND-CRT study was a prospective, randomized, double-blinded, multicenter, noninferiority trial. Patients were randomized in a 2:1 fashion to receive weekly, automatic CRT optimization with a SonR contractility sensor (LivaNova, Paris, France) versus an echo-guided optimization of AV and VV timings (72). The SonR contractility sensor records endocardial acceleration that correlates strongly with LV dP/dtmax, a measure of cardiac contractility. The primary efficacy endpoint was the rate of clinical response (patients alive, without adjudicated HF-related events, with improvement in New York Heart Association functional class or quality of life) at 12 months. The study randomized 998 patients. Response rate was 75.0% in the SonR group versus 70.4% in the Echo group (mean difference: 4.6%; 95% CI: 1.4% to 10.6%; $p < 0.001$ for a noninferiority margin of 10.0%). At an overall mean follow-up of 548 days, SonR was associated with a 35% risk reduction in HF hospitalization (HR: 0.65; 95% CI: 0.46 to 0.92; log-rank $p < 0.01$).

The AdaptivCRT algorithm automatically adjusts AV and VV delays on the basis of frequent evaluation of the patient's underlying intrinsic AV conduction (74). Specifically, the algorithm provides LV-only pacing synchronized to a spontaneous RV activation when intrinsic AV conduction is normal or BiV pacing when AV conduction is prolonged. The Adaptive CRT clinical trial demonstrated that this novel algorithm for delivering CRT was at least as effective as protocol-driven echocardiographic optimization. The time to first HF admission was found to be similar for aCRT patients and patients who underwent traditional echocardiographic optimization. Recently, Starling et al. (75) showed that for HF hospitalizations, the 30-day readmission rate was 19.1% (17 of 89 patients) in the aCRT group and 35.7% (15 of 42 patients) in the Echo group (odds ratio: 0.41; 95% CI: 0.19 to 0.86; $p < 0.02$). For all-cause hospitalization, the 30-day readmission rate was 14.8% (35 of 237 patients) in the aCRT group compared with 24.8% (39 of 157 patients) in the Echo group (odds ratio: 0.54; 95% CI: 0.31 to 0.94; $p < 0.03$). The risk of readmission after HF or all-cause index hospitalization with aCRT was also significantly reduced beyond 30 days. These results emphasized that use of the aCRT algorithm was associated with a significant reduction in the probability of a 30-day readmission after both HF and all-cause hospitalizations.

Finally, recent dog experiments showed the potential to calculate VCGs from nonpaced leads in the heart and to use the area of the determined QRS complex to optimize AV and VV delay (76). The smallest QRS area coincided with the setting, which resulted in the best hemodynamic effect. This idea was based on data that AV delays result in the smallest QRS area on the body surface and that VCG coincides with the best hemodynamic effect of CRT in patients (77). This opens the possibility of using this biomarker for continuous and ambulatory optimization.

ASSESSMENT OF RESIDUAL MECHANICAL DYSSYNCHRONY

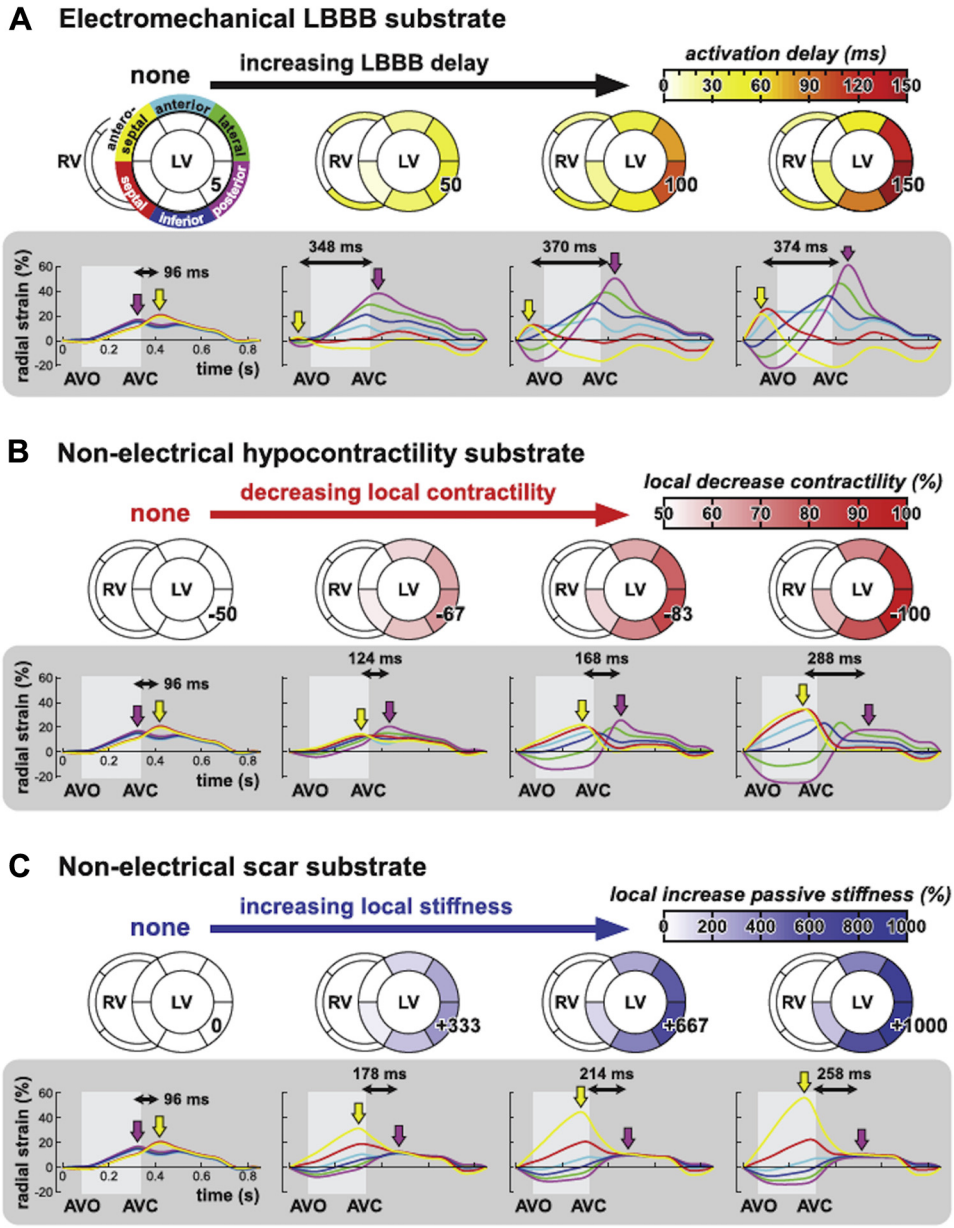
Restoration of more uniform distribution of LV myocardial strain is an expected effect of CRT, which is associated with improvement in LV function and survival (78). Data on patterns of residual myocardial dyssynchrony after CRT are limited. An echocardiographic subanalysis of MADIT-CRT (78) and subsequently by Tayal et al. (79) demonstrated a significant association between changes in mechanical dyssynchrony in patients treated with CRT and the occurrence of serious ventricular arrhythmias. Patients with new-onset dyssynchrony or persistent dyssynchrony after CRT showed a poor prognosis even after controlling for other known baseline predictors. These findings indicate that more attention to the change in mechanical contraction after CRT may further improve the benefit of CRT for patients.

COMPUTER MODEL-ASSISTED PATIENT SELECTION AND CRT APPLICATION

Computer models can contribute in several ways to improve clinical practice: better understanding of

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1203–19

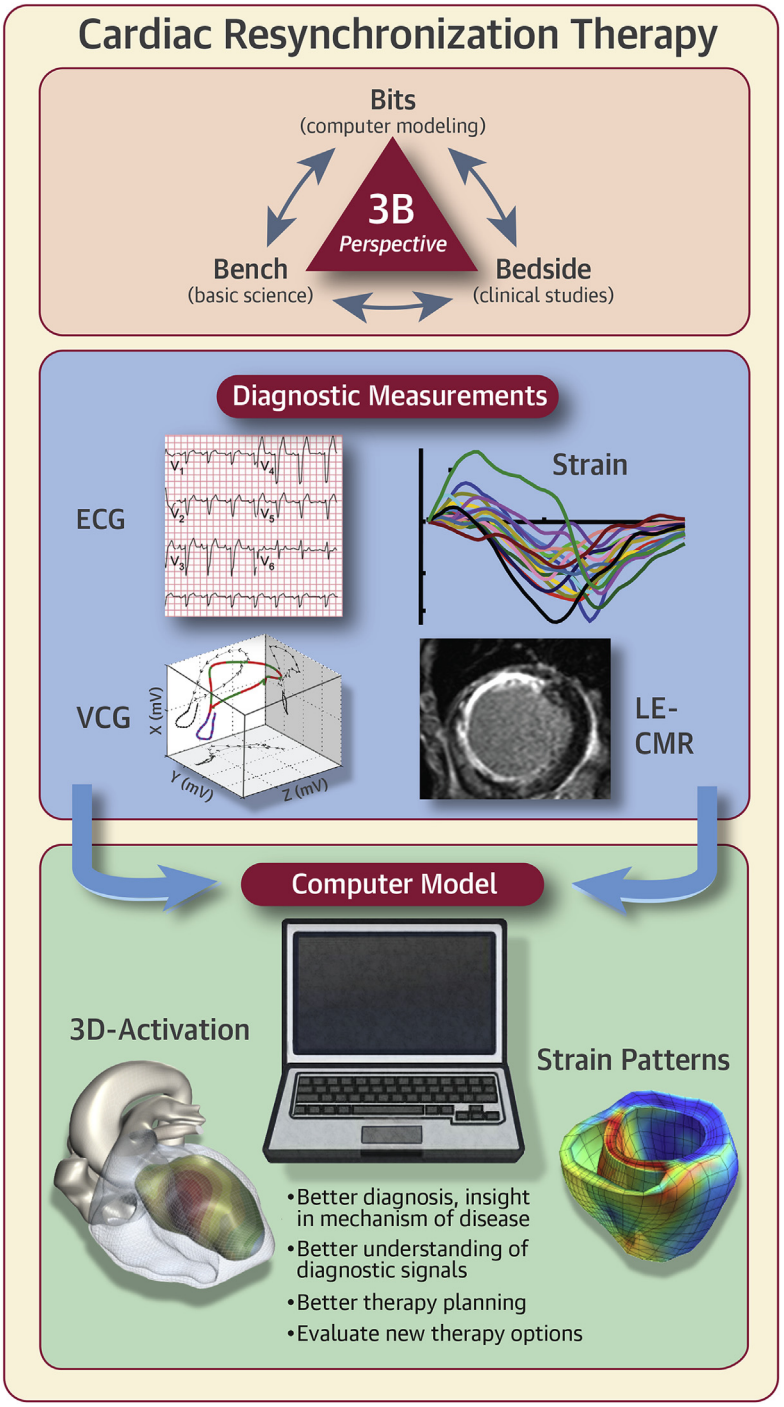
FIGURE 5 Discrimination Between an Electromechanical and Nonelectrical Substrates of Mechanical Dyssynchrony



Simulated substrates of mechanical discoordination, created by the CircAdapt model. **(A)** An electromechanical LBBB substrate is simulated as a septal-to-free wall gradient in activation delay. **(B)** A nonelectrical hypocontractility substrate simulated as a septal-to-free wall gradient in contractility. **(C)** A nonelectrical scar substrate simulated by adding a septal-to-free wall gradient in passive stiffness to the hypocontractility substrate is shown in **B**. All 3 substrates caused peak-to-peak radial strain delay, but the pattern of mechanical discoordination differs considerably between the substrates. Peak septal **(yellow arrow)** and posterior **(purple arrow)** radial strains were used to quantify peak-to-peak radial strain delay **(black double-headed arrows)**. AVC = aortic valve closure; AVO = aortic valve opening; LV = left ventricle; RV = right ventricle; other abbreviation as in Figure 4. Reproduced with permission from Lumens et al. (33).

mechanisms of disease and therapy; better interpretation of diagnostic measurements; and altogether better planning of the therapy in the individual patient by virtual delivery of therapy. Such models can also be used to improve the design of clinical trials. Currently, there are even developments to create cohorts of virtual patients for performing clinical trials in silico (80). The field of CRT is ideal for applying

CENTRAL ILLUSTRATION **Possible, in Part Future, Applications of Computer Models in CRT**



Auricchio, A. et al. J Am Coll Cardiol EP. 2017;3(11):1203–19.

(Upper panel) The concept of the 3B-perspective. **(Middle panel)** Various diagnostic tools for better stratification of cardiac resynchronization therapy (CRT) patients, ranging from standard 12-lead electrocardiogram (ECG) to vectorcardiography (VCG), speckle tracking strains and late enhancement-cardiac magnetic resonance (LE-CMR). **(Bottom panel)** Feeding a computer model with patient-specific diagnostic data can provide patient-specific "fingerprints" of cardiac electromechanics. This may help in better diagnosis and understanding of the mechanism of disease, better understanding of diagnostic signals under baseline conditions, and may lead to better therapy planning and evaluation of novel therapy options.

computer models because conceptual integration of all electrophysiological, contractile, and circulatory properties of a patient are too complex for the human brain. However, these models may be appropriately handled by high-performing computers and sophisticated mathematical algorithms that are capable of delivering simulations in a clinical usable timing.

Computer models of the dyssynchronous heart range from relatively simple 2-dimensional models of cardiac contraction and hemodynamics (81) to highly advanced 3-dimensional models that contain fiber orientation, molecular properties of ion channels, myocardial contraction, and body surface ECG (82–85). A good example of model-improved insight in disease mechanism and diagnosis is that of understanding of septal wall motion abnormalities, known as septal flash and septal rebound stretch (33,81). In the past, it was debated whether these paradoxical motions were caused by a transseptal pressure gradient or by early septal contraction. By varying myocardial and hemodynamic properties in computer models, it could be demonstrated that the slow and late contraction of the LV lateral wall were the key determinants of the septal wall motion abnormality. These models also showed that time to peak strain is not a reliable estimate of true (model-imposed) dyssynchrony, but that indexes of strain patterns (e.g., septal rebound stretch and systolic stretch index) might be better predictors of CRT response (33,86,87). This was further supported by a recent study from this group, which showed that heterogeneity in electrical activation, contractility, and stiffness could all lead to high values of time-to-peak shortening, but with different strain patterns (**Figure 5**). The Circadapt model also predicted that the slope and intercept of the relation between time of onset of electrical activation and peak shortening characterized myocardial stiffness and contractility, respectively (88).

Electrophysiological models have been used to construct impulse conduction throughout the ventricles based on the body surface ECG and position of the heart in the chest of the patient (85) or animal (89). In the latter animal study, strains were also calculated, as well as the benefit of CRT. Patient-specific modeling of the effect of CRT in such detailed models was established in studies that had few patients (90). Such patient-specific modeling has been achieved in hundreds of patients using the simpler and mathematically faster CircAdapt model (33,34).

With respect to application of resynchronization therapy, model studies provided understanding as to why LV pacing could be equivalent to BiV pacing (33), to what extent patients with RBBB could benefit from CRT (16), or why endocardial CRT could be superior to conventional epicardial CRT (50), and finally, under what conditions MPP could improve acute hemodynamic benefit compared with conventional BiV pacing (91). The ultimate goal for the application of modeling for CRT would be to develop a full model of the heart of an individual patient in a way that does not disturb clinical workflow, to plan the best position for the pacing leads, and to test the effect of CRT ahead of implantation of the device (**Figure 5, Central Illustration**). For the simpler models, this might be just around the corner, whereas routine clinical application of a more complex fully coupled electromechanical model might last another decade.

CONCLUSIONS

After decades of clinical use, CRT can be considered an established therapy. Despite that, there are still multiple open questions to be addressed that shall further improve the proportion of patients who respond to CRT. Progress in better understanding the profound relationship between electrical and mechanical disorder in HF patients with ventricular conduction abnormalities is of paramount importance. In addition, the use of the most advanced computer modeling should help in providing mechanistic insights into CRT efficacy, which coupled to machine learning, might certainly help in solving complicated problems with big data by identifying interaction patterns among variables.

ADDRESS FOR CORRESPONDENCE: Dr. Angelo Auricchio, Division of Cardiology, Fondazione Cardiocentro Ticino, Via Tesserete 48, 6900 Lugano, Switzerland. E-mail: angelo.auricchio@cardiocentro.org.

REFERENCES

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606–19.

2. Benjamin EJ, Blaha MJ, Chiuve SE, et al., American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017; 135:e146–603.

3. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

4. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

5. Auricchio A, Stellbrink C, Sack S, et al., for the Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026–33.

6. Linde C, Gold MR, Abraham WT, et al., for the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J 2013;34:2592–9.

7. Moss AJ, Hall WJ, Cannom DS, et al., for the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart failure events. N Engl J Med 2009;361:1329–38.

8. Tang AS, Wells GA, Talajic M, et al., for the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385–95.

9. Kirk JA, Kass DA. Cellular and molecular aspects of dyssynchrony and resynchronization. Heart Fail Clin 2017;13:29–41.

10. van Middendorp LB, Kuiper M, Munts C, et al. Local microRNA-133a downregulation is associated with hypertrophy in the dyssynchronous heart. ESC Heart Fail 2017;4:241–51.

11. Zareba W, Klein H, Cygankiewicz I, et al., MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.

12. Reddy VY, Miller MA, Neuzil P, et al. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: the SELECT-LV study. J Am Coll Cardiol 2017;69:2119–29.

13. Tomlinson DR, Bashir Y, Betts TR, Rajappan K. Accuracy of manual QRS duration assessment: its importance in patient selection for cardiac resynchronization and implantable cardioverter defibrillator therapy. Europace 2009;11:638–42.

14. Vancura V, Wichterle D, Ulc I, Šmíd J, Brabec M, Zárybnická M, Rokyta R. The variability of automated QRS duration measurement. Europace 2017;19:636–43.

15. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011;107:927–34.

16. Auricchio A, Lumens J, Prinzen FW. Does cardiac resynchronization therapy benefit patients with right bundle branch block: cardiac resynchronization therapy has a role in patients with right bundle branch block. Circ Arrhythm Electrophysiol 2014;7:532–42.

17. Fantoni C, Kawabata M, Massaro R, et al. Right and left ventricular activation sequence in patients with heart failure and right bundle branch block: a detailed analysis using three-dimensional non-fluoroscopic electroanatomic mapping system. J Cardiovasc Electrophysiol 2005;16:112–9.

18. Hara H, Oyenuga OA, Tanaka H, et al. The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy. Eur Heart J 2012;33:2680–91.

19. Vernooy K, van Deursen CJ, Strik M, Prinzen FW. Strategies to improve cardiac resynchronization therapy. Nat Rev Cardiol 2014;11:481–93.

20. Gold MR, Singh JP, Ellenbogen KA, et al. Interventricular electrical delay is predictive of response to cardiac resynchronization therapy. J Am Coll Cardiol EP 2016;2:438–47.

21. Auricchio A, Fantoni C, Regoli F, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 2004;109:1133–9.

22. Ploux S, Lumens J, Whinnett Z, et al. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle branch block morphology. J Am Coll Cardiol 2013;61:2435–43.

23. Cluitmans MJM, Bonizzi P, Karel J, et al. In vivo validation of electrocardiographic imaging: evaluation of noninvasively reconstructed epicardial potentials, electrograms and isochrones. J Am Coll Cardiol EP 2017;3:232–42.

24. Johnson WB, Vatterott PJ, et al. Body surface mapping using an ECG belt to characterize electrical heterogeneity for different left ventricular pacing sites during cardiac resynchronization: relationship with acute hemodynamic improvement. Heart Rhythm 2017;14:385–91.

25. Engels EB, Vegh EM, van Deursen CJM, Vernooy K, Singh JP, Prinzen FW. T-wave area as an additional predictor of response to cardiac resynchronization therapy. J Cardiovasc Electrocardiol 2015;26:176–83.

26. Mafi Rad M, Gilbert WM, Wijntjens GMW, et al. Vectorcardiographic QRS area identifies delayed left ventricular lateral wall activation determined by electroanatomic mapping in patients undergoing cardiac resynchronization therapy. Heart Rhythm 2016;13:217–25.

27. Maass AH, Vernooy K, Wijers SC, et al. Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study. Europace 2017 Feb 27 [E-pub ahead of print].

28. Tereshchenko LG, Cheng A, Park J, et al., SMART-AV Trial Investigators. Novel measure of electrical dyssynchrony predicts response in cardiac resynchronization therapy: results from the SMART-AV Trial. Heart Rhythm 2015;12:2402–10.

29. Stankovic I, Prinz C, Ciarka A, et al. Long-term outcome after CRT in the presence of mechanical dyssynchrony seen with chronic RV pacing or intrinsic LBBB. J Am Coll Cardiol Img 2017;10:1091–9.

30. Ruschitzka F, Abraham WT, Singh JP, et al., EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395–405.

31. Bax JJ, Delgado V, Sogaard P, et al. Prognostic implications of left ventricular global longitudinal strain in heart failure patients with narrow QRS complex treated with cardiac resynchronization therapy: a subanalysis of the randomized EchoCRT trial. Eur Heart J 2017;38:720–6.

32. Risum N, Tayal B, Hansen TF, et al. Identification of typical left bundle branch block contraction by strain echocardiography is additive to electrocardiography in prediction of long-term outcome after cardiac resynchronization therapy. J Am Coll Cardiol 2015;66:631–41.

33. Lumens J, Leenders GE, Cramer MJ, et al. Mechanistic evaluation of echocardiographic dyssynchrony indices: patient data combined with multiscale computer simulations. Circ Cardiovasc Img 2012;5:491–9.

34. Leenders GE, Lumens J, Cramer MJ, et al. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: analysis of patient data using a computer model. Circ Heart Fail 2012;5:87–96.

35. Lumens J, Tayal B, Walmsley J, et al. Differentiating the electromechanical substrate responsive to cardiac resynchronization therapy from non-electrical dyssynchrony substrates by computer-assisted regional strain analysis. Circ Cardiovasc Imag 2015;8:e003744.

36. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. Circ Heart Fail 2013;6:427–34.

37. Kydd AC, Khan FZ, Watson WD, Pugh PJ, Virdee MS, Dutka DP. Prognostic benefit of optimum left ventricular lead position in cardiac resynchronization therapy: follow-up of the TARGET Study Cohort (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy). J Am Coll Cardiol HF 2014;2:205–12.

38. Leyva F, Foley PW, Chalil S, et al. Cardiac resynchronisation therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:29.

39. Bakos Z, Ostenfeld E, Markstad H, et al. A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy. Europace 2014;16:1779–86.

40. Behar J, Mountney P, Toth D, et al. Real time X-MRI guided left ventricular lead implantation for targeted delivery of cardiac resynchronization therapy. J Am Coll Cardiol EP 2017;3:803–14.

41. Providencia R, Rogers D, Papageorgiou N, et al. Long-term results of triventricular versus biventricular pacing in heart failure: a propensity

matched comparison. J Am Coll Cardiol EP 2016;2:825–35.

42. Leclercq C, Gadler F, Kranig W, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. J Am Coll Cardiol 2008;51:1455–62.

43. Lenarczyk R, Kowalski O, Kukulski T, et al. Midterm outcomes of triple-site vs. conventional cardiac resynchronization therapy: a preliminary study. Int J Cardiol 2009;133:87–94.

44. Rogers DP, Lambiase PD, Lowe MD, Chow AW. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. Eur J Heart Fail 2012;14:495–505.

45. Ogano M, Iwasaki YK, Tanabe J, et al. Antiarrhythmic effect of cardiac resynchronization therapy with triple-site biventricular stimulation. Europace 2013;15:1491–8.

46. Forleo GB, Di Biase L, Bharmi R, et al. Hospitalization rates and associated cost analysis of cardiac resynchronization therapy with an implantable defibrillator and quadripolar vs. bipolar left ventricular leads: a comparative effectiveness study. Europace 2015;17:101–7.

47. Turakhia MP, Cao M, Fischer A, et al. Reduced mortality associated with quadripolar compared to bipolar left ventricular leads in cardiac resynchronization therapy. J Am Coll Cardiol EP 2016;2:426–33.

48. Pappone C, Ćalović Ž, Vicedomini G, et al. Multipoint left ventricular pacing improves acute hemodynamic response assessed with pressure-volume loops in cardiac resynchronization therapy patients. Heart Rhythm 2014;11:394–401.

49. Zanon F, Baracca E, Pastore G, et al. Multipoint pacing by a left ventricular quadripolar lead improves the acute hemodynamic response to CRT compared with conventional biventricular pacing at any site. Heart Rhythm 2015;12:975–81.

50. Pappone C, Ćalović Ž, Vicedomini G, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: twelve-month follow-up study. Heart Rhythm 2015;12:1250–8.

51. Zanon F, Marcantoni L, Baracca E, et al. Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year. Heart Rhythm 2016;13:1644–51.

52. St. Jude Medical. St. Jude Medical announces MultiPoint Pacing IDE study results during late-Breaker at Heart Rhythm 2016. Available at: http://media.sjm.com/newsroom/news-releases/news-releases-details/2016/St-Jude-Medical-Announces-MultiPoint-Pacing-IDE-Study-Results-During-Late-Breaker-at-Heart-Rhythm-2016/default.aspx. Accessed June 3, 2017.

53. Sterliński M, Sokal A, Lenarczyk R, et al. In heart failure patients with left bundle branch block single lead multispot left ventricular pacing does not improve acute hemodynamic response to conventional biventricular pacing. A multicenter prospective, interventional, non-randomized study. PLoS One 2016;11:e0154024.

54. Hyde ER, Behar JM, Claridge S, et al. Beneficial effect on cardiac resynchronization from left ventricular endocardial pacing is mediated by early access to high conduction velocity tissue: electrophysiological simulation study. Circ Arrhythm Electrophysiol 2015;8:1164–72.

55. Strik M, van Middendorp LB, Vernooy K. Animal models of dyssynchrony. J Cardiovasc Transl Res 2012;5:135–45.

56. Van Deursen C, Van Geldorp I, Rademakers LM, et al. Left ventricular endocardial pacing improves resynchronization therapy in canine LBBB hearts. Circ Arrhyth Electrophysiol 2009;2:580–7.

57. Derval N, Steendijk P, Gula LJ, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. J Am Coll Cardiol 2010;55:566–75.

58. Spragg DD, Dong J, Fetics BJ, et al. Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. J Am Coll Cardiol 2010;56:774–81.

59. Shetty AK, Sohal M, Chen Z, et al. A comparison of left ventricular endocardial, multisite, and multipolar epicardial cardiac resynchronization: an acute haemodynamic and electroanatomical study. Europace 2014;16:873–9.

60. Morgan JM, Biffi M, Gellér L, et al., ALSYNC Investigators. ALternate Site Cardiac ResYNChronization (ALSYNC): a prospective and multicentre study of left ventricular endocardial pacing for cardiac resynchronization therapy. Eur Heart J 2016;37:2118–27.

61. Auricchio A, Delnoy PP, Butter C, et al., for the Collaborative Study Group. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study. Europace 2014;16:681–8.

62. Narula OS. Longitudinal dissociation in the His bundle. Bundle branch block due to asynchronous conduction within the His bundle in man. Circulation 1977;56:996–1006.

63. Upadhyay GA, Tung R. Selective versus non-selective His bundle pacing for cardiac resynchronization therapy. J Electrocardiol 2017;50:191–4.

64. Sharma PS, Ellenbogen KA, Trohman RG. Permanent His bundle pacing: the past, present, and future. J Cardiovasc Electrophysiol 2017;28:458–65.

65. Teng AE, Lustgarten DL, Vijayaraman P, et al. Usefulness of His bundle pacing to achieve electrical resynchronization in patients with complete left bundle branch block and the relation between native QRS axis, duration, and normalization. Am J Cardiol 2016;118:527–34.

66. Ajijola OA, Upadhyay G, Macias C, Shivkumar K, Tung R. Permanent His-bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. Heart Rhythm 2017;14:1353–61.

67. Mills RW, Cornelussen RN, Mulligan LJ, et al. Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency. Circ Arrhyth Electrophysiol 2009;2:571–9.

68. Mafi-Rad M, Luermans JGLM, Blaauw Y, et al. Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum. Circ Arrhythm Electrophysiol 2016;9:e003344.

69. Rademakers LM, van Hunnik A, Kuiper M, et al. A possible role for pacing the LV septum in cardiac resynchronization therapy. J Am Coll Cardiol EP 2016;2:413–22.

70. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS, FREEDOM Steering Committee. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: the Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial. Am Heart J 2010;159:944–8.

71. Ellenbogen KA, Gold MR, Meyer TE, et al. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation 2010;122:2660–8.

72. Brugada J, Delnoy PP, Brachmann J, et al., for the RESPOND CRT Investigators. Contractility sensor-guided optimization of cardiac resynchronization therapy: results from the RESPOND-CRT trial. Eur Heart J 2017;38:730–8.

73. Singh JP, Abraham WT, Chung ES, et al. Clinical response with adaptive CRT algorithm compared with CRT with echocardiography-optimized atrioventricular delay: a retrospective analysis of multicentre trials. Europace 2013;15:1622–8.

74. Martin DO, Lemke B, Birnie D, et al., Adaptive CRT Study Investigators. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. Heart Rhythm 2012;9:1807–14.

75. Starling RC, Krum H, Bril S, et al. Impact of a novel adaptive optimization algorithm on 30-day readmissions: evidence from the Adaptive CRT Trial. J Am Coll Cardiol HF 2015;3:565–72.

76. Engels EB, Strik M, van Middendorp LB, Kuiper M, Vernooy K, Prinzen FW. Prediction of optimal cardiac resynchronization by vectors extracted from electrograms in dyssynchronous canine heart. J Cardiovasc Electrophys 2017;28:944–51.

77. van Deursen CJM, Vernooy K, Dudink E, et al. Vectorcardiographic parameters as novel predictors of response to cardiac resynchronization therapy. J Electrocardiogr 2015;48:45–52.

78. Kutyifa V, Pouleur AC, Knappe D, et al. Dyssynchrony and the risk of ventricular arrhythmias. J Am Coll Cardiol Img 2013;6:432–44.

79. Tayal B, Gorcsan J 3rd, Delgado-Montero A, et al. Mechanical dyssynchrony by tissue Doppler cross-correlation is associated with risk for complex ventricular arrhythmias after cardiac

resynchronization therapy. J Am Soc Echocardiogr 2015;28:1474–81.

80. Avicenna Roadmap: In Silico Clinical Trials. Available at: http://avicenna-alliance.com/avicenna-roadmap/. Accessed October 30, 2017.

81. Lumens J, Delhaas T, Kirn B, Arts T. Three-wall segment (TriSeg) model describing mechanics and hemodynamics of ventricular interaction. Ann Biomed Eng 2009;37:2234–55.

82. Niederer SA, Lamata P, Plank G, et al. Analyses of the redistribution of work following cardiac resynchronisation therapy in a patient specific model. PLoS One 2012;7:e43504.

83. Panthee N, Okada J, Washio T, et al. Tailor-made heart simulation predicts the effect of cardiac resynchronization therapy in a canine model of heart failure. Med Image Anal 2016;31:46–62.

84. Sermesant M, Chabiniok R, Chinchapatnam P, et al. Patient-specific electromechanical models of the heart for the prediction of pacing acute effects in CRT: a preliminary clinical validation. Med Image Anal 2012;16:201–15.

85. Potse M, Krause D, Kroon W, et al. Patient-specific modeling of cardiac electrophysiology in heart-failure patients. Europace 2014;4:iv56–61.

86. Remme EW, Niederer S, Gjesdal O, et al. Factors determining the magnitude of the pre-ejection leftward septal motion in left bundle branch block. Europace 2016;18:1905–13.

87. Walmsley J, Huntjens PR, Prinzen FW, Delhaas T, Lumens J. Septal flash and septal rebound stretch have different underlying mechanisms. Am J Physiol 2016;310:H394–403.

88. Kroon W, Lumens J, Potse M, et al. In vivo electromechanical assessment of heart failure patients with prolonged QRS duration. Heart Rhythm 2015;12:1259–67.

89. Villongco CT, Krummen DE, Omens JH, McCulloch AD. Non-invasive, model-based measures of ventricular electrical dyssynchrony for predicting CRT outcomes. Europace 2016;18 Suppl 4:iv104–12.

90. Crozier A, Blazevic B, Lamata P, et al. The relative role of patient physiology and device optimisation in cardiac resynchronisation therapy: a computational modelling study. J Mol Cell Cardiol 2016;96:93–100.

91. Niederer SA, Shetty AK, Plank G, Bostock J, Razavi R, Smith NP, Rinaldi CA. Biophysical modeling to simulate the response to multisite left ventricular stimulation using a quadripolar pacing lead. Pacing Clin Electrophysiol 2012;35:204–14.

KEY WORDS cardiac magnetic resonance, cardiac resynchronization therapy, left bundle branch block, outcome, pacing

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC quiz for this article.